Antimicrobial Resistance in Developing Countries

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Policy Center for Biomedical Research
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Former DG ICMR, India
Global Trends
Deaths attributable to antimicrobial resistance every year compared to other major causes of death

- Tetanus: 60,000
- Cholera: 100,000 - 120,000
- Measles: 130,000
- AMR: 10,000,000
- Road traffic accidents: 1,200,000
- Diarrhoeal disease: 1,400,000
- Diabetes: 1,500,000
- Cancer: 8,200,000

Source: Review on Antimicrobial Resistance 2014
Deaths attributable to antimicrobial resistance every year by 2050

North America: 317,000
Latin America: 392,000
Europe: 390,000
Africa: 4,150,000
Asia: 4,730,000
Oceania: 22,000

Source: Review on Antimicrobial Resistance 2014
Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries.
Antibiotic consumption is increasing in developing countries...

**Per capita total antibiotic use, retail sector, 2005-2010**

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
Once an antibiotic is introduced, resistance is not far behind...

Non-prescription use of antimicrobials

Figure 2: Frequency of non-prescription use of antimicrobials in the general population based on published works in small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

CDDEP
THE CENTER FOR
Disease Dynamics,
Economics & Policy
WASHINGTON DC • NEW DELHI

Morgan et al, Lancet ID, 2011
Hospital use of carbapenems is rapidly growing

Per capita total carbapenem use, hospital sector, 2005-2010

Source: Based on data obtained under license from IMS Health MIDAS™ (January 1999-December 2010); IMS Health Incorporated. All Rights Reserved.
Potential loss of in GDP, % fall compared to baseline scenario in 2050

Source: KMPG project
INDIA
Status Paper: Rationalizing antibiotic use to limit antibiotic resistance in India+
Global Antibiotic Resistance Partnership (GARP) - India Working Group

Determinants of antibiotic prescribing:

- Lack of appropriate knowledge
- Lack of trust in or delayed lab results
- Desire to meet patient demand
- Fear of clinical failure
- Economic incentives
- Unstable/inadequate drug supply
- Peer norms
- Marketing influence
- Traditional beliefs about antibiotics

Number of studies that identified these determinants

Indian J Med Res 134, September 2011, pp 281-294
Action needed a global level to tackle emerging threats like NDM-1
<table>
<thead>
<tr>
<th>Isolate and resistance determinants</th>
<th>Total (%)</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
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<tr>
<td></td>
<td></td>
<td>No. of strains</td>
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<td>3</td>
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<td>0</td>
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<td>0</td>
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ICU
Jan., 2008 - Dec., 2010 Blood Isolates
3 Yrs. (n = 1928)

- Candida sps, 522
- Staphylococci, 506
- Klebsiella, 245
- Acinetobacter, 210
- Enterococci spp., 135
- E. coli, 116
- Pseudomonas aeruginosa, 90
- Enterobacter, 38
- Staph. aureus, 37
- Strept. pneumoniae, 18
- Salmonella typhi, 11

Table I: Trends of isolation rates, antimicrobial consumption and resistance *K.pneumoniae*

<table>
<thead>
<tr>
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<td>80</td>
<td>94</td>
<td>89</td>
<td>81</td>
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<td>98</td>
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<td>90</td>
<td>77</td>
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<td>89</td>
<td>76</td>
<td>59</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>80</td>
<td>64</td>
<td>83</td>
<td>82</td>
<td>66</td>
<td>81</td>
<td>86</td>
<td>64</td>
<td>84</td>
<td>0.411</td>
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<tr>
<td>Piperacillin+ Tazobactum</td>
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<td></td>
<td></td>
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<td>Carbapenems</td>
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<td>1.7</td>
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<td>0</td>
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<td>3</td>
<td>47</td>
<td>52</td>
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<tr>
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<td>74</td>
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<td>58</td>
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<td></td>
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<td>Amp C</td>
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<td></td>
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<td>8%</td>
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<tr>
<td>Carbapenemase producer</td>
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<td>51%</td>
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Table I: Trends of isolation rates, antimicrobial consumption *E.coli*

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<tr>
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<td>8%</td>
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<tr>
<td>Carbapenemase producer</td>
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<td>15%</td>
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</table>

Association between carbapenem consumption and resistance in *P. aeruginosa* and *A. baumannii* (SGRH)

$p$ value for *A. baumannii* $< 0.5$

Goel & Wattal, JAC, May 17; 2011
"The Chennai Declaration" named after the city where the meeting took place, is the consensus evolved out of the meeting and co-authored by representatives of various medical societies. The document is based on realistic goals and objectives, with a deep understanding of the background Indian scenario.
Antimicrobial Resistance Research and Surveillance network: India

Indian Council of Medical Research

Source: Dr. Kamini Walia ICMR
Antimicrobial Resistance Research and Surveillance

• Antimicrobial Resistance Research and Surveillance

• Antimicrobial Stewardship Program
  – Treatment guidelines
  – Infection control policy document
  – Prescription practices
  – Focus on infectious diseases
Antimicrobial Research and Surveillance Network at ICMR

• Nodal centres are focal points for six pathogenic groups:
  – *Enterobacteriaceae* / sepsis (PGIMER)
  – Fungal pathogens (PGIMER)
  – Gram negative non-fermenters (CMC)
  – Enteric fever organisms (AIIMS)
  – Diarrhoeagenic organisms (CMC)
  – MRSA, Enterococcus (JIPMER)

• 15 Regional Centres (RC) proposed

**Major imperatives: Standardisation and uniformity**
Updates.....

• Data collection at nodal centers initiated on September 1, 2013
  – Almost 18,000 isolates tested
• SOPs (bacteriology and mycology) available at ICMR website
• Data managed by the Bioinformatics team at ICMR HQs
**Shigella spp**

- High resistance to nalidixic acid
- 50 % R to norfloxacin and ampicillin
- Association of ESBL genes with *qnr* genes – rare among Indian isolates
- $\text{bla}_{\text{CTX-M-15}}$ occurrence in *Shigella spp* increases the threat for spread of cephalosporin resistance among Enterobacteriaceae

<table>
<thead>
<tr>
<th>Organism (n = 31)</th>
<th>Genes for sulfonamide resistance</th>
<th>Genes for β-lactam resistance</th>
<th>Genes for quinolone resistance</th>
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<tr>
<td></td>
<td>dhfr1a</td>
<td>Sul II</td>
<td>$\text{bla}_{\text{OXA}}$</td>
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<td>S. flexneri (n = 22)</td>
<td>22</td>
<td>15</td>
<td>12</td>
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<tr>
<td>S. sonnei (n = 6)</td>
<td>6</td>
<td>5</td>
<td>-</td>
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Salmonella typhi

- **S. typhi** multidrug resistance (MDR): ampicillin, chloramphenicol and trimethoprim – sulfamethoxazole - downward trend
- High resistance to **FQ, cephalosporins** in *S. typhi* is increasingly reported
Non-fermenting gram negative bacilli (NFGNB)

- *Acinetobacter* species 60% isolates, *Pseudomonas* species 24%, *Strophomonas* species 4%, *Burkholderia* species 4%.
- All isolates of *P. aeruginosa* were susceptible to colistin, followed by imipenem (85%), amikacin (80%), ciprofloxacin (80%), piperacillin-tazobactam (58%) and meropenem (50%).
- *A. baumanii* isolates showed maximum susceptibility was to colistin (99%) followed by imipenem (53%) and meropenem (53%).
No. of genes identified in CRO multiplex PCR reaction

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>NC</th>
<th>‘n’</th>
<th>SPM</th>
<th>IMP</th>
<th>VIM</th>
<th>NDM</th>
<th>OXA-48 Like</th>
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<td>0</td>
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ICMR Antimicrobial Stewardship Program: Survey of Practices, 2014

- 20 Hospitals: 13 public and 7 private
- AMSP documents in 4/20 hospitals
- Accreditations better in private hospitals
- Infection control document in 20/20
- Comprehensive treatment guidelines missing in most hospitals
  - Syndrome specific guidelines frequently available
- AMSP not linked with IT system in most hospitals
- Most hospitals do not have infectious disease physicians and clinical pharmacists
### Antimicrobial Surveillance and Research network

#### E. coli from blood

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<th>PGIMER</th>
<th>CMC Vellore</th>
<th>JIPMER</th>
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<tr>
<td>Cefotaxime</td>
<td>&lt;10</td>
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<td>Amikacin</td>
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#### Klebsiella spp from blood

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<th>JIPMER</th>
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<tr>
<td>Cef-sulbatam</td>
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<td>60</td>
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<tr>
<td>Amikacin</td>
<td>&lt;40</td>
<td>60</td>
<td>42</td>
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<tr>
<td>Ceftazidime</td>
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<td>40</td>
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<tr>
<td>Pip-Tazo</td>
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<td>45</td>
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Trends in Anti-microbiome Pan Indian Distribution of Pneumococcal Serotypes

PIDOPS study: Dr. K L Ravi

Multidrug Resistance: 26%
Trends in Anti-microbiome

PIDOPS study: Dr. K L Ravi
Foreign collaborations

- **National Institute of Allergy and Infectious Diseases, NIH, USA**
  - Systems biology
  - Epidemiology of neonatal sepsis
  - Clinical trials for new entities

- **Center for Disease Control, USA**
  - Strengthening infection control

- **Research Council Norway, Norway**
  - Methods for assessment of the burden of resistance
  - Integrated project surveillance systems for AMR and antibiotic use in humans and/or animals.
  - Ecological, evolutionary and molecular studies of AMR in clinical and non-clinical environments.
Antimicrobial Resistance – Cadila Approach

Collaborative effort with UK organization

• Develop antibiotic resistance breakers (ARB) to rejuvenate known – approved antibiotics.

• Antibiotic Resistance Breakers
  – Improves efficacy of approved antibiotics
    • Effective against resistant organism
    • Faster killing
    • Least Chance of developing resistance
    • Effective against multiplying as well as non-multiplying organisms

• Known compounds (approved drugs) as well as Novel compounds with no/minimal antibacterial activity
ARB and MDR Gram –ve organisms

Faster Killing of resistant organisms
ARB and MRSA infection

Faster Killing of resistant organisms
Need for proactive actions to assist developing countries in strengthening systems to address AMR risks

- Strengthening national and international interdisciplinary cooperation and developing holistic strategies and action plans
- Improving regulatory frameworks based on internationally agreed principles and standards (Codex, OIE)
- Reducing the need for antimicrobials in animal husbandry, by improving animal health disease prevention and good practices along the chain
- Strengthening food and human surveillance systems for AMR and the quantities of all antimicrobials being used at the national level
- Raising awareness (among veterinarians, value chain actors including producers and the public) about AMR
- Developing appropriate policies/guidance on the prudent and responsible use of antimicrobials in animal husbandry
- Supporting research to generate data on the prevalence and trends in AMR, as well as supporting risk assessment, risk management and risk communication in the AMR area
THANK YOU